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(54) Suspension aerosol formulations

(57) A pharmaceutical suspension aerosol formulation consisting of a therapeutically effective amount of micronised albuterol sulphate, propellant selected from HFC134a, HFC 227 and mixtures thereof and ethanol in an amount of from 5 to 15% by weight of the aerosol formulation.

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Description

[0001] This invention relates to pharmaceutical aerosol formulations and in particular to pharmaceutical suspension aerosol formulations containing albuterol sulfate.

[0002] Pharmaceutical suspension aerosol formulations currently use a mixture of liquid chlorofluorocarbons as the propellant. Fluorotrichloromethane, dichlorodifluoromethane and dichlorotetrafluoroethane are the most commonly used propellants in aerosol formulations for administration by inhalation.

[0003] Chlorofluorocarbons (CFCs), however, have been implicated in the destruction of the ozone layer and their production is being phased out. Hydrofluorocarbon 134a (HFC 134a, 1,1,1,2-tetrafluoroethane) and hydrofluorocarbon 227 (HFC 227, 1,1,1,2,3,3,3-heptafluoropropane) are viewed as being more ozone friendly than many chlorofluorocarbon propellants; furthermore, they have low toxicity and vapor pressures suitable for use in aerosols.

[0004] Patent Applications WO 91/11495 and WO 91/11496 (both by Weil) describe pharmaceutical suspension aerosol formulations comprising a medicinal agent, optionally a surfactant, and a propellant mixture containing 1,1,1,2,3,3,3-heptafluoropropane and one or more additional components, e.g., pentane, butane, propellant 134a, propellant 11, propellant 125, or propellant 152a.

[0005] European Patent Office Publication 0 384 371 (Heiskel) describes solution aerosols in which 1,1,1,2,3,3,3-heptafluoropropane or its mixture with propane, butane, isobutane, dimethyl ether, or 1,1-difluoroethane serves as the propellant. The application does not, however, disclose suspension aerosols or pharmaceutical aerosol formulations.

[0006] European Patent Application 89.312270.5 (Purewal et al.) discloses, inter alia, aerosol formulations comprising a medicament, 1,1,1,2-tetrafluoroethane, a surface active agent, and at least one compound having higher polarity than 1,1,1,2-tetrafluoroethane.

[0007] U.S. Pat. No. 2,868,691 (Porush et al.) discloses aerosol formulations comprising a medicament, a halogenated lower alkane propellant, and a cosolvent which assists in dissolving the medicament in the propellant. The chemical formula for the propellant given in Col. 2, lines 6-16, generically embraces HFC 134a and HFC 227. Examples of cosolvents disclosed include ethanol and diethyl ether.

[0008] U.S. Pat. No. 3,014,844 (Thiel et al.) discloses aerosol formulations comprising a micronized medicament, a halogenated lower alkane propellant and a surface-active agent to assist in the suspension of the medicament in the propellant. The chemical formula for the propellant given in Col. 4, lines 17-28, generically embraces HFC 134a and HFC 227.

[0009] Patent Application WO 90/01454 (Greenleaf et al.) discloses aerosol compositions having HFC 134a as the propellant and comprising a medicament coated with a non-perfluorinated surface active dispersing agent. This application describes control formulations containing only HFC 134a and 0.866 percent by weight of a drug.

[0010] Albuterol sulfate is a relatively selective beta-2 adrenergic bronchodilator. It is available in a variety of dosage forms including tablets, syrups and formulations suitable for inhalation. For example; VENTOLIN™ Inhalation Aerosol (commercially available from Allen & Hansburys) is a metered dose aerosol unit containing a microcrystalline suspension of albuterol (free base) in propellant (a mixture of trichloromonofluoromethane and dichlorodifluoromethane) with oleic acid. VENTOLIN ROTOCAPS™ for Inhalation (commercially available from Allen & Hansburys) contain a mixture of microfine albuterol sulfate with lactose and are intended for use with a specially designed device for inhaling powder. VENTOLIN™ Solution for Inhalation (commercially available from Allen & Hansburys) is an aqueous solution of albuterol sulfate intended for use with a nebulizer.

[0011] This invention provides a pharmaceutical suspension aerosol formulation consisting of a therapeutically effective amount of micronised albuterol sulphate, propellant selected from HFC 134a, HFC 227 and mixtures thereof and ethanol in an amount of from 5 to 15% by weight of the aerosol formulation.

[0012] This invention also provides an aerosol canister containing a formulation as described above in an amount sufficient to provide a plurality of therapeutically effective doses of the drug. Also provided is a method of preparing a formulation as described above, comprising the steps of: (i) combining an amount of the drug sufficient to provide a plurality of therapeutically effective doses and the propellant in an amount sufficient to propel from an aerosol canister a plurality of therapeutically effective doses of the drug; and (ii) dispersing the drug in the propellant. This invention further provides a method of treating a mammal having a condition capable of treatment by inhalation, comprising the step of administering by inhalation a formulation as described above to the mammal.

[0013] This invention also provides a method for inducing bronchodilation in a mammal, comprising administering to the mammal a formulation as described above by inhalation.

[0014] The term "suspension aerosol formulation" as used herein refers to a formulation in which the drug is in particulate form and is substantially insoluble in the propellant.

[0015] Amounts expressed herein in terms of percent refer to percent by weight based on the total weight of the formulation.

[0016] The formulations of the invention contain, a drug in a therapeutically effective amount, that is, an amount such that the drug can be administered as an

aerosol (e.g., topically or by oral or nasal inhalation) and cause its desired therapeutic effect with one dose, or less preferably several doses, from a conventional valve, e.g., a metered dose valve. "Amount" as used herein refers to quantity or to concentration as appropriate to the context. The amount of a drug that constitutes a therapeutically effective amount varies according to factors such as the potency, efficacy, and the like, of the particular drug, on the route of administration of the formulation, and on the device used to administer the formulation. A therapeutically effective amount of a particular drug can be selected by those of ordinary skill in the art with due consideration of such factors. Particularly in formulations of the invention intended for oral inhalation into the lungs, the drug is preferably micronized, i.e., about 90 percent or more of the particles have a diameter of less than about 10 microns, in order to assure that the particles can be inhaled into the lungs.

[0017] The particular amount of drug that will remain suspended in a formulation of the invention for a time sufficient to allow reproducible dosing of the drug depends to some extent on the nature of the particular drug, e.g., its density, and on the particular propellant used in the formulation. Generally, however, it has been found that when drug concentrations of less than about 0.1 percent are used in a formulation of the invention the drug flocculates to some degree but generally does not settle or cream to the extent that the suspension becomes unsuitable for use as an aerosol formulation, e.g., in a metered dose inhaler. Therefore as regards drug concentration such formulations are acceptably homogeneous.

[0018] When drug concentrations greater than about 0.1 percent but less than about 0.5 percent are used in a formulation of the invention it is sometimes seen that the drug flocculates considerably in the formulation and therefore might have an increased tendency to cream or settle. As discussed below in connection with the propellant component of the formulations of the invention, in these instances it is preferable to select the propellant in a manner that minimizes creaming and settling of the drug in order to assure that the formulation is acceptably homogeneous as regards drug concentration.

[0019] As drug concentration increases, e.g., beyond about 0.5 percent, the tendency of the drug to flocculate generally increases also. However, the volume occupied by the flocculated drug also increases and the flocculated drug begins to occupy substantially all of the volume of the formulation. In such instances the flocculated drug often shows a lesser tendency to cream or settle. As regards drug concentration such formulations are acceptably homogeneous.

[0020] Generally the concentration of the drug in a formulation of the invention is preferably less than about 0.1 percent, more preferably less than about 0.08 percent, and most preferably less than about 0.05 percent. Accordingly, it is preferred according to this invention that the drug have a potency such that concentrations less than about 0.1 percent, more preferably less than about 0.08 percent, and most preferably less than about 0.05 percent, are therapeutically effective. The drug used in the formulations of the invention is albuterol sulphate.

[0021] The propellant in a formulation of the invention can be HFC 134a, HFC 227, or a mixture thereof in any proportion. The propellant is present in an amount sufficient to propel a plurality of doses from a metered dose inhaler The density of HFC 134a differs from the density of HFC 227. Therefore the density of the propellant can be adjusted within limits. by using mixtures of HFC 134a and HFC 227 in order to accommodate the density of the drug. It is sometimes preferred that the propellant be selected such that the propellant density is as closely matched as possible to the drug density in order to minimize tendencies for the drug to settle or cream, particularly when drug concentration is greater than 0.1 percent or when the drug concentration is between about 0.1 percent and about 0.5 percent.

[0022] The albuterol sulfate formulations of the invention contain a therapeutically effective amount of micronized albuterol sulfate. Preferably micronized albuterol sulfate constitutes about 0.2 to about 0.5 percent by weight, more preferably from about 0.35 to about 0.42 percent by weight of the aerosol formulation.

[0023] Ethanol can optionally be included in such an albuterol sulfate formulation of the invention. When ethanol is present it constitutes from about 0.1 to about 20 percent by weight, preferably from about 5 to about 15 percent by weight of the formulation.

[0024] Certain preferred albuterol sulfate suspension aerosol formulations of the invention comprise HFC 227 as substantially the only propellant. Typically the propellant constitutes the remainder of the weight of the formulation once the albuterol sulfate and the optional surfactant and/or ethanol are accounted for. Accordingly the propellant is generally present in an amount of at least about 75 percent by weight based on the total weight of the formulation.

[0025] Preferred albuterol sulfate formulations of the invention exhibit substantially no growth in particle size or change in crystal morphology of the albuterol sulfate over a prolonged period, are substantially and readily redispersible, and upon redispersion do not flocculate so quickly as to prevent reproducible dosing of albuterol sulfate.

[0026] Generally the formulations of the invention can be prepared by combining (i) the drug in an amount sufficient to provide a plurality of therapeutically effective doses; and (ii) the propellant in an amount sufficient to propel a plurality of doses from an aerosol canister; and dispersing the drug in the propellant. The drug can be dispersed using a conventional mixer or homogenizer, by shaking, or by ultrasonic energy. Bulk formulation can be transferred to smaller individual aerosol

vials by using valve to valve transfer methods or by using conventional cold-fill methods.

[0027] The albuterol sulfate suspension aerosol formulations of this invention can be prepared by combining the albuterol sulfate and the propellant and dispersing the albuterol sulfate in the propellant using a conventional mixer or homogenizer. Ethanol can be added to the propellant along with the albuterol sulfate.

[0028] Aerosol canisters equipped with conventional valves, preferably metered dose valves, can be used to deliver the formulations of the invention. It has been found, however, that selection of appropriate valve assemblies for use with aerosol formulations is dependent upon the particular surfactants or adjuvants used (if any), on the propellant, and on the particular drug being used. Conventional neoprene and buna valve rubbers used in metered dose valves for delivering conventional CFC formulations often have less than optimal valve delivery characteristics and ease of operation when used with formulations containing HFC 134a or HFC 227. Moreover, conventional CFC formulations generally contain a surfactant in part as a lubricant for the valve stem. Some formulations of the invention, however, do not contain a surfactant or a lubricant. Therefore certain formulations of the invention are preferably dispensed via a valve assembly wherein the diaphragm is fashioned by extrusion, injection molding or compression molding from a thermoplastic elastomeric material such as FLEXOMER™ DFDA 1137 NT7 polyolefin, FLEXOMER™ DFDA 1138 NT polyolefin, FLEXOMER™ DEFD 8923 NT polyolefin, FLEXOMER™ GERS 1085 NT polyolefin, FLEXOMER™ DFDA 1163 NT7 polyolefin, FLEXOMER™ 1491 NT7 polyolefin, FLEXOMER™ 9020 NT7 polyolefin, FLEXOMER™ 9042 NT polyolefin (Union Carbide), C-FLEX™ thermoplastic elastomer R70-001, C-FLEX™ thermoplastic elastomer R70-051, C-FLEX™ thermoplastic elastomer R70-041, C-FLEX™ thermoplastic elastomer R70-085, C-FLEX™ thermoplastic elastomer R70-003, or C-FLEX™ thermoplastic elastomer R70-026 (Concept Polymer Technologies), or a blend of two or more thereof.

[0029] Conventional aerosol canisters, e.g., those of aluminum, glass, stainless steel, or polyethylene terephthalate, can be used to contain a formulation of the invention.

[0030] The formulations of the invention can be delivered to the lung by oral inhalation in order to effect bronchodilation or in order to treat a condition. susceptible of treatment by inhalation, e.g., asthma, chronic obstructive pulmonary disease.

Claims

1. A pharmaceutical suspension aerosol formulation consisting of a therapeutically effective amount of micronised albuterol sulphate, propellant selected from HFC134a, HFC 227 and mixtures thereof and ethanol in an amount of from 5 to 15% by weight of the aerosol formulation.

2. A pharmaceutical suspension aerosol formulation according to Claim 1 in which the albuterol sulphate is present in an amount of from 0.2 to 0.5% by weight of the aerosol formulation.

3. A pharmaceutical suspension aerosol formulation according to Claim 2 in which the albuterol sulphate is present in an amount of from 0.35 to 0.42% by weight of the aerosol formulation.

4. A metered dose aerosol canister containing a formulation as claimed in any preceding Claim in an amount sufficient to provide a plurality of therapeutically effective doses of the drug.

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EUROPEAN SEARCH REPORT

Application Number
EP 00 12 3885

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.7)
A,D	EP 0 372 777 A (RIKER) 13 June 1990 (1990-06-13) * claims * * page 5, line 18 - line 19 * * page 5, line 34 * * examples 1-6,19-24 *	1-4	A61K9/00 A61K9/12 A61K31/137
A,D	WO 91 11495 A (BOEHRINGER INGELHEIM) 8 August 1991 (1991-08-08) * claims 1,2,6,7,12 * * example 6 *	1-4	
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TECHNICAL FIELDS SEARCHED (Int.Cl.7)
A61K

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
THE HAGUE	31 January 2001	Scarponi, U

CATEGORY OF CITED DOCUMENTS

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